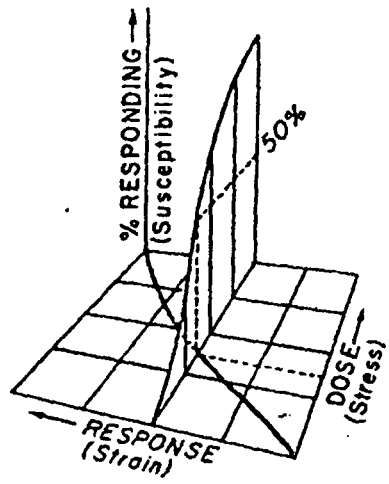

Fig. 4. [Modified from Hatch (61); reprinted by permission of publisher; copyright 1968, American Medical Association.] Dose response for a population. The curve on the horizontal plane portrays the dose-response relationship for a population of susceptibility such that 50 per cent respond to the dose indicated by the dotted line. If only 25 per cent were responsive to that dose, the curve would be proportionately displaced downward toward the dose axis; if 75 per cent were responsive, it would be appropriately displaced upward.

tem, or the physical fitness of the person (less fit persons ventilate more for a given work load). Alternatively, susceptibility might be considered in the immunologic sense.

A major problem, however, in applying the dose-response concept to the study of asbestos-related disease in animals and man lies in the measurement of dose. Presumably, the relevant dose (in Hatch's terms, the dose delivered at the critical site in the body) is the amount of asbestos dust and fiber retained in the lung, i.e., the amount inhaled less the amount exhaled and/or cleared from the lung. Although estimates of the amount inhaled can be derived from direct measurements of dust and fiber in the working environment and from ventilation volume, there is no practical way to measure the amount of dust exhaled and/or cleared from the lung, either in the laboratory animal or in man. Thus, at best, it is possible to measure (or estimate) only the first one half of the dose equation, i.e., the concentration and amount of dust inspired (in Hatch's terms, the magnitude of exposure to external conditions that give rise to stress).

This shortcoming is perhaps less crucial under experimental conditions in which animals can be raised throughout life in environments with different, but known and constant, dust concentrations. Such studies have, in general, shown dose relationships for amount of fibrosis and cancer risk (62). In addition, it seems possible that mathematical computation, taking into account intermittency and pulse exposures (42), may enable future studies to make even better estimates of dose.

In epidemiologic studies, estimates of dose have had to be much more crude, being based on the number of years of service in an industry (63–68); the number of years since first exposure (63, 69, 70); or the total years of exposure, together with an estimate of the dustiness of a worker's job (71–79); or cumulative dust exposure calculated from dust concentrations for given jobs. Doses may be calculated for each individual worker on the basis of his or her work history (80–95), or for groups of workers in given jobs in a given industry (96–98). In all of these studies, there has been the problem of calculating the dose for workers whose exposure usually extended into the remote past, with information about dust concentrations being at best scanty and incomplete and in most instances nonexistent.

Despite the shortcomings of the methods for estimating dose, a relationship of estimated dose to response has, nevertheless, been a consistent finding (table 4). This consistency has been true with exposures encountered in mining, manufacturing, and secondary usage, including removal of old asbestos insulation. Furthermore, it applied to all of the responses examined, i.e., lung fibrosis, as reflected by symptoms (64, 77, 92), lung function (64, 78, 84, 87) and radiographic changes (65, 69, 88, 95), and lung cancer, as reflected in mortality statistics (63, 66–68, 71, 74, 77, 79–83, 85, 93). For mesothelioma, in which much less exposure seems to be capable of producing a response in certain circumstances (see neighborhood and domestic exposure), there is also some evidence for a dose effect using fiber counts in the lungs at autopsy as a measure of exposure. A more complete discussion of dose-response relationships follows in the sections devoted to various asbestos-related lung diseases.

It must be pointed out that although dose-response relationships are evident to a greater or lesser extent for all responses, the degree of correlation is surprisingly low, perhaps because one seldom, if ever, finds more than a 50 per cent